REMARKS

I. Status of the Claims

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 318-323, 325 and 326 were pending in the July 22, 2010 Office Action. Claims 318-323 were withdrawn and claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 were examined therein. With this Reply, claims 265, 290, and 303 are amended and claims 245, 248-251, 253-255, 260 and 264 are newly canceled. The amendments and cancelations are made without prejudice or disclaimer.

II. Rejections under 35 U.S.C. § 102

(a) Claims 245, 248-251, 253-255, 260, 264, 265, 268, 272, 284, 290 and 296 are rejected under 32 U.S.C. 102(b) as anticipated by Izant et al. (Chimeric Antisense RNAs, pp. 183-195 in Gene Regulation: Biology of Antisense RNA and DNA 1992). Applicants request reconsideration and withdrawal of this rejection in light of the following discussion.

Applicants first note that claims 245, 248-251, 253-255, 260, and 264 are canceled. With respect to claims 264 and dependent claims 265, 268, 272, 284, 290 and 296, the Office Action asserts that, although Izant does not teach constructs where a portion of the snRNA is removed, "...[t]he claims do not explicitly recite particular nucleic acid sequences, nor do they explicitly state removal of the native sequences, and so displacement of the original sequences of the native U2 snRNA by intervening sequences would be reasonably encompassed by the broad genus claimed."

In response, Applicants note that the claims as amended are directed to

> An isolated nucleic acid construct which when present in a cell acts as a template for the synthesis of a nucleic acid comprising (i) a nuclear localization sequence comprising a portion of U1, U2 or U4 snRNA, said portion of U1, U2 or U4 snRNA comprising sequences for (a) at least two stem loops present at the 3' end of native U1, U2 or U4 snRNA, and (b) a reimportation signal and (ii) an antisense nucleic acid sequence, wherein said antisense nucleic acid sequence

replaces stem-loop sequences removed from said U1, U2 or U4 snRNA that are not in said two stem loops present at the 3' end of said snRNA.

Claim 265. The claims as amended thus specify the removal of sequences that are replaced by the antisense nucleic acid, as described and fully supported in the specification. As such, the skilled artisan would understand that the claims are directed to a construct where "said antisense nucleic acid sequence replaces stem-loop sequences **removed** from said U1, U2 or U4 snRNA that are not in said two stem loops present at the 3' end of said snRNA". Since Izant et al. does not teach such a construct, that reference does not anticipate the claims. Applicants therefore respectfully request withdrawal of the rejection of claims 264, 265, 268, 272, 284, 290 and 296 under 35 U.S.C. 102(b) as being anticipated by Izant et al.

(b) Claims 245, 248-251, 253-255, 264, 272 and 284 are rejected under 32 U.S.C. 102(e) as anticipated by Meador et al. (US 5,547,862). Applicants request reconsideration and withdrawal of this rejection in light of the following discussion.

Claim 272 and 274 are the only claims in this rejection that are not canceled. Both of those claims are dependent on claim 265. As such, the rejected claims are directed to constructs encoding an snRNA nuclear localization sequence, a reimportation signal and an antisense nucleic acid sequence. However, Meador et al. do not teach or suggest any constructs encoding an snRNA. As such, Meador et al. do not anticipate claims 272 and 274. Withdrawal of the rejection of claims 272 and 274 under 35 U.S.C. 102(e) as being anticipated by Meador et al. is therefore respectfully requested.

III. Rejection under 35 U.S.C. § 103

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 272, 284, 288-290, 296, 299, 303, 304, 308- 313 and 324-326 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meador et al. (discussed under **II.(b) above**) and Izant et al. (discussed under **II.(a) above**) the combination in view of Calabretta et al. (US

5,734,039) and Binkley et al. (Nucleic Acids Research, 1995, 23:3198-3205), the combination in further view of Craig et al. (WO 95/08635) and Alul et al. (US 5,532,130).

With regard to claims 265, 268, 272, 284, 288-290, 296, Applicants note from the discussion under **II.** above, that neither Izant et al. nor Meador et al. teach or suggest a construct encoding an snRNA nuclear localization sequence, a reimportation signal and an antisense nucleic acid sequence, where the antisense nucleic acid sequence replaces removed (*i.e.*, deleted) snRNA sequences. Additionally, neither Calabretta et al., Binkley et al., Crai et al. nor Alul et al. teach or suggest a construct comprising an antisense nucleic acid sequence that replaces removed or deleted snRNA sequences, since none of those references are related to snRNA sequences, or the replacement of stem-loop sequences. As such, the combination of references do not teach or suggest each element of claims 265, 268, 272, 284, 288-290, 296 and therefore do not make those claims obvious.

With regard to claims 299, 303, 304, 308, 312, 313, 325 and 326, directed to

> An isolated multi-cassette nucleic acid construct comprising at least three copies of a promoter, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each promoter, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral RNAs in a cell or binds to a specific viral protein, wherein each specific nucleic acid so produced binds to different target nucleic acid sequences.

(claim 299) and similar constructs comprising more than one copy or an snRNA promoter or bacteriophage promoter (claim 325), or three copies of a promoter producing specific nucleic acids directed to HIV RNAs or proteins (claim 326), Applicants first note that Izant et al. do not teach or suggest a construct comprising at least three, or even two, copies of a promoter. Additionally, in any constructs described by Meador et al. that have multiple promoter copies, those promoters are <u>different</u> promoters, not three <u>copies</u> of a promoter, as claimed.

Calabretta et al. also do not describe a construct with <u>three</u> copies of a promoter. As discussed in the previous response and in the Office Action, Calabretta et al. only teach "a composition for introducing two different antisense oligonucleotides specific for

two different genes in a cell." (Office Action at page 9). Indeed, Calabretta et al. is primarily concerned with administration of synthetic oligonucleotides. There is only a brief mention therein of a construct having a first promoter and a second promoter (see Col. 9, lines 14-30 of Calabretta et al.). Additionally, with respect to claim 325, Calabretta et al. do not discuss the use of an snRNA promoter or a bacteriophage promoter.

As discussed in the Office Action, neither Binkley et al., Craig et al., nor Alul et al. teach or suggest a construct having three copies of a promoter.

The Action combines the references by asserting "[i]t would have been obvious to design a multi-cassette nucleic acid construct comprising the U2 snRNP promoter construct taught previously by Izant, and relying on the teachings of multiple promoter constructs taught previously by Meador because the elements required for producing (secondary) recombinant nucleic acids, including antisense and sense nucleic acids, using either the U2 or bacteriophage promoters were well known in the art." Office Action at page 10. Applicants disagree, since none of the cited references teach or suggest using more than one **copy** of the **same** promoter in the construct, which is an element of each of the subject claims. Indeed, Binkley et al. and Craig et al. do not even discuss the use of any promoters. The skilled artisan would not have a motivation to use more than one copy of the same promoter since the cited references all teach that use of different promoters, when more than one promoter is discussed, is completely effective for the methods described therein. Thus, the very concept of using more than one copy of the same promoter is not introduced by any of the cited references, and none of the cited references provide any motivation for using more than one copy of a particular promoter, rather than the universally taught different promoters in widespread use at the time of filing. Applicants thus assert that the combination of references do not teach or suggest at least the claim element of multiple copies of a single promoter, and provide no motivation for using such a construct. Therefore, the combination of references do not make the instant claims obvious. Withdrawal of this rejection is thus respectfully requested.

IV. Rejection under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 290, 296, 299, 303, 304, 308, 312, 313, 325 and 326 are rejected under 35 U.S.C. 112, first paragraph, written description requirement. The Office Action specifically asserts

> The specification and claims do not adequately describe the various genera comprising 1.) any snRNA comprising sequences for stem loops present at the 3' end of any native snRNA, and which comprise any re-importation signal or which comprise any antisense replacing sequences that participated in stem-loop formation in the native form of any snRNA; ii.) any cellular protein comprising any nuclear localizing protein or cytoplasmic localizing protein; iii.) any decoy protein binding to any protein required for viral assembly or viral replication.
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> ...
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> ...the instant disclosure, at the time of filing, does not provide enough description of an adequate number of species for the broad genera claimed, and purported secondary structure consensus does not ensure the generation of functioning expression cassettes for all of the species claimed. The example provided in the instant disclosure does not fill the gap of information needed about what deletions would be tolerated in the snRNA structures and still allow for retaining the features of promoter function and nuclear re-importation activities.

Office Action at pp. 14-15. Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

Applicants again note that claims 245, 248-251, 253-255, 260, 264 are canceled. Additionally, although the Office Action discusses lack of written description relating to decoy proteins, Applicants note that none of the claims as amended recite "decoy proteins".

Regarding claims 265 and dependent claims 268, 270, 272, 284, 290 and 296, Applicants assert that the specification provides a description of the invention to the full extent of the claims. For example, a discussion of the structure of snRNAs, the presence and extent of the re-importation signal, and methods for inserting antisense RNA therein according to the claims is provided at pp. 9-10, 14-16, 101-104, and 162-164, and FIGS. 41-44. The retention of the region of the snRNA that includes the two

stem loops that are most 3' (for example the C and D stem loops) as well as the Sm region, known to be required for snRNA processing and nuclear re-importation, assures import of the inserted antisense to the nucleus. Further, extensive discussions of U1, U2 and U4, including structural information and location of the Sm regions for those snRNAs is provided in Zieve and Sauterer, 1990, Biochemistry and Molecular Biology 25:1-46, and information about the snRNA genes and their promoters is provided in Dahlberg and Lund, 1988, pp. 38-70 in Structure and Function of Major and Minor Small Nuclear Ribonucleoprotein Particles, M. Birnsteil, Ed., both incorporated by reference at page 9 of the specification, and provided with the Information Disclosure Statement dated March 7, 2003. Given the extensive information provided as referenced above, the skilled artisan would understand that the invention is adequately described for any U1 U2 or U4 snRNA, since those sequences are extensively described, including the structures of the stem loops and the Sm regions, for example in Zieve and Sauterer (see, e.g., FIG. 1 on page 3 therein), and that reference additionally teaches that those snRNAs are highly conserved.

Applicants also note that the Zieve and Sauterer and Dahlberg and Lund references discussed above, are review articles that cite numerous articles concerning the effect of deletions in U1, U2 and U4, and the effect of those deletions on the biological functions of those snRNAs. As such, the skilled artisan could identify a multitude of regions in any U1, U2 or U4 snRNA, where the antisense nucleic acid could replace stem loop regions while assuring nuclear re-importation according to the claims.

Regarding claims 299, 303, 304, 308, 312, 313, 325 and 326, Applicants note that the specification provides an extensive description of those inventions at pp. 104-110, with examples provided at pp. 164-182 (Examples 27-32) and figures referred to therein (FIGS. 44-51). Additionally, the state of the art at the time of filing was such that production of the claimed multi-cassette nucleic acid constructs was routine in the art, since production of the claimed constructs requires molecular biology methods that were routine at the time. That state of the art also included extensive knowledge about numerous promoters, viral RNAs, and compounds that bind to viral RNAs or proteins.

Indeed, an example of the latter prior art includes Binkley et al., 1995, Nucleic Acids Research 23:3198-3205, cited in the obviousness rejection in the Office Action.

In view of the above discussion, Applicants assert that the claims were described in the specification, with such support from the state of the art, that the skilled artisan would understand that the inventors had possession of the claimed inventions at the time of filing for their full scope. Withdrawal of the written description rejection under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

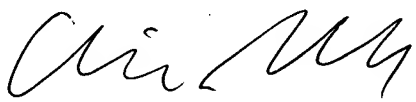
V. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections of record and examination of withdrawn claims 321 and 322 as provided under MPEP 821.04, since the withdrawn claims have all the limitations of allowable claim 299.

Applicants authorize the United States Patent and Trademark Office to charge all fees required to maintain pendency of this application, including the extension of time and Request for Continued Examination fees, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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